

# Effect of L-Tryptophan on Spasmodic Torticollis

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**SUMMARY:** *The effect of L-tryptophan, a precursor of serotonin, and placebo were studied in eight patients with spasmodic torticollis. L-Tryptophan (5g po as a single dose) which increased free plasma tryptophan 20-53 fold improved only one out of six patients. Two out of three patients, including the subject who improved following an oral load of tryptophan, improved with L-tryptophan combined with nicotinamide, a tryptophan pyrrolase inhibitor, when administered for 1-3 weeks. However, the magnitude of clinical improve-*

*ment was not impressive. Our findings suggest that impairment of serotonergic function is not a general finding in spasmodic torticollis though it may play a minor role in the manifestation of this movement disorder in some patients. The present study emphasizes some of the difficulties in evaluating therapeutic response, namely, the intrinsic variability of the disorder, the response to placebo in some subjects and the limitations of methods for measuring change.*

**RÉSUMÉ:** *Nous avons étudié l'effet du L-tryptophane, un précurseur de la sérotonine, et d'un placebo chez 8 patients souffrant de torticollis spasmodique. Le L-tryptophane (5 g, p.o.; dose unique) augmente la concentration plasmatique du tryptophane libre de 20 à 53 fois, mais n'améliora qu'un seul patient. Deux de 3 patients (y compris celui qui fut préalablement aidé) se sont améliorés lorsque le tryptophane fut combiné à la nicotinamide (un inhibiteur de la tryptophane pyrrolase) pendant des périodes de 1 à 3 semaines. Cependant*

*l'ampleur de l'amélioration est minime. Nos résultats indiquent que le rôle d'un déficit en sérotonine dans le torticollis n'est pas général, même s'il peut jouer un rôle mineur dans les manifestations cliniques de cette maladie chez certains patients. Nous avons aussi montré la difficulté d'une telle étude, particulièrement dans l'évaluation de la réponse thérapeutique ou au placebo, ainsi que la variabilité intrinsèque de la maladie et les limites de la méthode de mesure des changements.*

## INTRODUCTION

The abnormality underlying the development of spasmodic torticollis (ST) and the nature of the presumed neurotransmitter dysfunction is unknown (Lal, 1979). Mori and associates (Mori et al., 1975) reported improvement in seven out of eight patients following L-5-hydroxytryptophan (L-5HTP), the immediate precursor of serotonin (5-HT). This raises the possibility that impairment of 5-HT function may play a role in the pathophysiology of ST. However, L-aromatic amino acid decarboxylase is located not only in 5-HT neurons but also in dopamine (DA) neurons (Andén et al., 1972). Accordingly, when 5-HTP is administered both 5-HT and DA function are altered. The latter arises by displacement of DA by the accumulation of 5-HT within DA neurons (Ng et al., 1972). In the present study we have investigated the role of 5-HT function in ST by administering a load of L-tryptophan. As tryptophan hydroxylase is selectively localized within 5-HT neurons (Joh et al., 1975) administration of L-tryptophan increases 5-HT only within 5-HT neurons (Aghajanian and Asher, 1971) and has no effect on DA function (Lal et al., 1980). This study represents a completion of preliminary investigations (Lal et al., 1979). In addition, we have looked at the therapeutic effect of L-tryptophan combined with nicotinamide. In the rat, nicotinamide is an inhibitor of tryptophan pyrrolase, the first enzyme in the major degradative pathway for tryptophan (Young and Sourkes, 1977). Nicotinamide had been recommended as a drug to inhibit the induction by tryptophan of tryptophan pyrrolase and thus prevent accelerated degradation of tryptophan when the latter is administered on a regular basis (Young and Sourkes, 1974).

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## PATIENTS AND METHODS

Six patients on no medication were administered, under blind conditions, L-tryptophan (5g po) or placebo (lactulose). Clinical details of the patients, #1, 4, 5, 6, 7 and 8, have been given elsewhere (Lal et al., 1979). Sixty minutes before drug administration a 19-gauge scalp vein needle was inserted into an arm vein and kept open with heparin-saline. Serial videotape recordings of one minute duration were made at -30, 0, 30, 60, 90, 120, 150 and 180 minutes. Tryptophan or placebo was administered immediately after the 0 minute recording. Just prior to each recording 10 ml of blood was drawn for estimation of total and free (non-albumin bound) plasma tryptophan. The tryptophan concentration in an ultrafiltrate of plasma was taken as the free plasma tryptophan concentration. The ultrafiltrate was obtained with an Amicon propellant pressurized ultrafiltration cell with UM membranes (nominal molecular weight cutoff 10,000) at 37°C and pH 7.4. Tryptophan in ultrafiltrate and plasma was measured by the method of Denckla and Dewey (1967). After placebo administration, blood samples were similarly drawn but later discarded.

Three patients, #2, 8 and 11 (Lal et al., 1979), were treated with L-tryptophan (Tryptan, © ICN) combined with nicotinamide daily for 3, 1 and 5 weeks, respectively. Subjects were aware of the treatment they were receiving. The response was compared with results obtained from prior placebo trials conducted under double-blind conditions. The dose in the first week was L-tryptophan 2g, nicotinamide 0.5g in two divided doses. Thereafter the doses of both were doubled.

An index of the intrinsic variability of the movement disorder in each patient was assessed by videotape recordings under basal conditions which were obtained over a period of several months.

The position of the patient for videotape recording was individualized. In patient #4, the duration the subject was able to maintain the head in a given position was measured. In the remaining five patients the fre-

quency of movements was counted. A global assessment of improvement was also made.

All tapes were assessed blind as to treatment code. Because of the variation in movement counts between subjects, the loading experiment data are plotted as percent change from the 0 minute recording except in subject #4. In subject #4 baseline values on the day of placebo and day of tryptophan load differed markedly and percent changes were of a different order of magnitude to the other 5 patients. Accordingly, the absolute data are given for this patient. Data were also looked at in terms of the number of standard deviations that individual recordings deviated from the serial basal recordings obtained for each subject. For some of the analyses, Student's t test was used.

## RESULTS

Basal recordings over a period of several months showed wide variation for each subject (Table 1). There were also differences in basal values recorded on the day of the tryptophan load and the day of receiving placebo. Following tryptophan administration there was a rapid increase in both free (Figure 1) and total tryptophan. The plasma free tryptophan increased from  $2.6 \pm 0.4$   $\mu\text{g/ml}$  (mean  $\pm$  SEM) to a mean individual peak value of  $65.2 \pm 11.1$   $\mu\text{g/ml}$ . Total tryptophan increased from  $13.6 \pm 1.0$   $\mu\text{g/ml}$  to a mean individual peak value of  $156.5 \pm 21.6$   $\mu\text{g/ml}$ .

Fluctuations from the 0 time recording were evident after both placebo and tryptophan (Figure 1). The mean individual nadir percent of

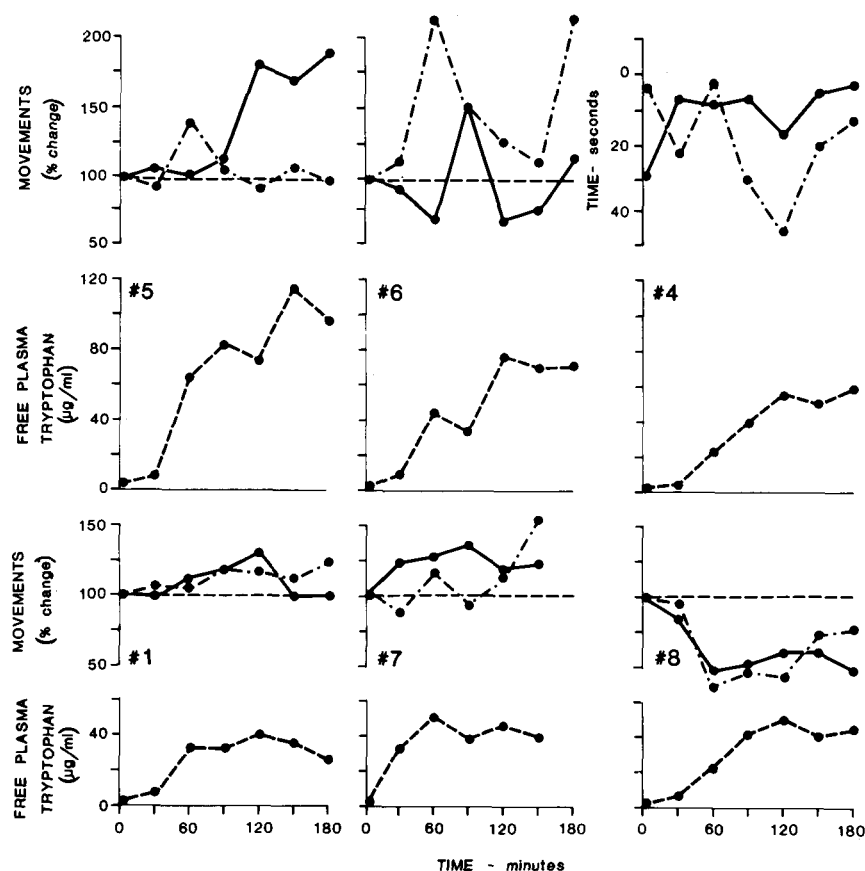


Figure 1—Effect of L-tryptophan on spasmodic torticollis. Patients received L-tryptophan (5g po) (●—●) or placebo (○—○) and the condition monitored on videotape and tryptophan concentrations (●—●) measured in plasma. In patients #1, 5, 6, 7 and 8, the percent change in movement frequency from time 0 min (100%) is plotted against time. In patient #4, the duration in seconds that the head could be maintained in a given position is plotted against time.

TABLE 1  
Variation In Movement Counts In Spasmodic Torticollis

Patient	x ± SD	Basal <sup>1</sup> N	Range	Movement Counts/Min Baseline <sup>2</sup>		Placebo	Treatment Tryptophan plus Nicotinamide
				Placebo	Tryptophan		
1	73 ± 21.9	20	44-114	50	53		
2	122 ± 8.3	13	105-136			120	102 <sup>4</sup>
4	13.9 ± 19.1 <sup>3</sup>	32	1.5-68 <sup>3</sup>	2.5 <sup>3</sup>	30 <sup>3</sup>		
5	43 ± 8.7	18	32-65	37	16 <sup>5</sup>		
6	25.2 ± 11	23	12-56	8	12		
7	30 ± 13.7	27	1-54	18	24		
8	201 ± 19.4	22	160-233	189	186	169	137 <sup>5</sup>
11	99.5 ± 25.3	20	43-144			93	82

<sup>1</sup>Serial basal recordings over a period of several months; N = number of recordings.

<sup>2</sup>Baseline values on day of placebo or tryptophan load

<sup>3</sup>Data presented as duration of maintaining head in a given position (seconds)

<sup>4</sup>>2 SD below serial basal values

<sup>5</sup>>3 SD below serial basal values

baseline counts after placebo was  $86 \pm 13.4\%$  (mean  $\pm$  SEM) and after tryptophan  $86.5 \pm 13.2\%$  (N = 5; P = NS). The mean individual peak percent above baseline movement counts after placebo was  $144.9 \pm 19.8\%$  and after tryptophan  $137.8 \pm 16.7\%$  (N = 5; P = NS). In only one of the six patients (#8) was there a sustained decrease in movements of 25% or more below the baseline value following tryptophan. From 60 to 180 minutes the movements were more than 2-5 SD below serial basal values. A similar decrease was also evident in this patient after placebo. However, though the decrease in frequency was similar after both treatments the decrease in amplitude was more noticeable after tryptophan than after placebo. Also, global assessment of improvement showed a more favorable response to tryptophan than to placebo. There was apparent worsening in two subjects (#5, #4) after tryptophan compared with placebo. However, the 0 minute recording on the day of tryptophan loading in subject #5 was more than 3 SD below the serial basal recordings and the highest frequency count after tryptophan closely approximated the mean of the serial basal recordings. In subject #4, the 0 minute recording showed a 12-fold difference between

the day of loading with tryptophan and the day of loading with placebo. Values noted after tryptophan were within the intrinsic variability established for this patient.

Following tryptophan plus nicotinamide two of the three patients, including the patient who improved following the tryptophan load, showed a decrease in movement counts which was more than 2 SD below serial basal recordings (Table 1). The magnitude of the decrease, however, was not clinically impressive. Neither patient was subjectively improved. Patient #11 complained that his neck was stiffer. This same subject complained of constipation, fearfulness, anxiety, tremor and dizziness which resulted in his terminating treatment. Neither subject noted any change in facility of conducting day-to-day physical activities.

#### DISCUSSION

Mori et al (1975) reported that the administration of L-5HTP, with or without amantadine, improved seven out of eight patients with ST who had been stereotactic surgery failures. L-5HTP enhances 5-HT and alters DA function. As amantadine alone, as well as antidopaminergic agents, are reported to improve ST (Lal et al., 1979),

the role of 5-HT mechanisms in the improvement noted by Mori and associates is unclear.

Human ventricular CSF tryptophan parallels changes in plasma free tryptophan (Young et al., 1976) and by inference brain tryptophan concentrations. Also, administration of tryptophan is known to increase central 5-HT turnover in man (Eccleston et al. 1970). In the present study L-tryptophan in a dose sufficient to increase plasma free tryptophan 20-53 fold above basal concentrations was used to increase 5-HT synthesis. Despite large elevations in plasma free tryptophan levels only one of the six patients examined showed improvement compared with placebo. Though two out of three patients showed a reduction in movement frequency when administered tryptophan combined with nicotinamide, the magnitude of change was not clinically impressive. The present findings suggest that impairment of central 5-HT function is not a general finding in ST though it may play a minor role in the manifestation of this movement disorder in some patients.

One issue that emerges from the present investigations is the difficulty in evaluating therapeutic response in patients with ST. These difficulties include the response to placebo in

some patients and problems in measuring change. Evaluation of a single variable such as frequency of involuntary movements may be insufficient to characterize the response adequately as amplitude of movement must also be considered. The latter is less easy to quantify by videotape recording than frequency. Also, improvement noted under the standardized conditions of videotape recording may not always provide an accurate reflexion of the disorder under conditions of daily living. A major problem in evaluating therapeutic response lies in the intrinsic variability of this disorder. Some idea of this variability is necessary in order to interpret apparent responses to drugs. In the present study the individual variability was assessed by obtaining a series of recordings under standardized conditions over several months.

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